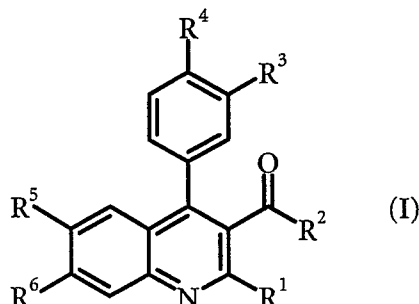


Quinoline as allosteric enhancers of the GABA-B receptors

The present invention relates to compounds of formula I



wherein

- R<sup>1</sup> is hydrogen, C<sub>1</sub>-C<sub>7</sub> alkyl, C<sub>1</sub>-C<sub>7</sub> haloalkyl, di(C<sub>1</sub>-C<sub>7</sub>)alkylamino, C<sub>3</sub>-C<sub>8</sub> cycloalkyl,  
 5 or 5 or 6 membered heterocycloalkyl;  
 R<sup>2</sup> is C<sub>1</sub>-C<sub>7</sub> alkyl, aryl, C<sub>1</sub>-C<sub>7</sub> alkoxy(C<sub>1</sub>-C<sub>7</sub>)alkyl, C<sub>1</sub>-C<sub>7</sub> haloalkyl or C<sub>3</sub>-C<sub>8</sub>  
 cycloalkyl;  
 R<sup>3</sup>, R<sup>4</sup> are each independently hydrogen, halo, hydroxy, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub>  
 haloalkoxy, di(C<sub>1</sub>-C<sub>7</sub>)alkylamino, C<sub>1</sub>-C<sub>7</sub> alkylsulfonyl, or 5 or 6 membered  
 10 heterocycloalkyl;  
 R<sup>5</sup> is hydrogen, halo, C<sub>1</sub>-C<sub>7</sub> alkyl, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> haloalkoxy, or aryloxy,  
 or is -NR<sup>7</sup>R<sup>8</sup> wherein R<sup>7</sup> and R<sup>8</sup> are C<sub>1</sub>-C<sub>7</sub> alkyl, or R<sup>7</sup> and R<sup>8</sup> may, together with  
 the nitrogen atom to which they are attached, form or a 4 to 8 membered  
 heterocycloalkyl group which may be substituted by one or more substituent(s)  
 15 selected from the group consisting of halo, C<sub>1</sub>-C<sub>7</sub> alkyl, C<sub>1</sub>-C<sub>7</sub> alkoxy, hydroxy,  
 phenyl and di(C<sub>1</sub>-C<sub>7</sub>)alkylamino;  
 R<sup>6</sup> is hydrogen or together with R<sup>5</sup> may form a 5 or 6 membered heterocycloalkyl  
 group which may be substituted by one or more halogen;  
 and pharmaceutically acceptable acid addition salts thereof,  
 20 excluding the following compounds:  
 1-(6-Chloro-2-methyl-4-phenyl-quinolin-3-yl)-ethanone;  
 1-(6-Bromo-4-phenyl-2-piperidin-1-yl-quinolin-3-yl)-ethanone;  
 1-[4-(4-Chloro-phenyl)-2-methyl-quinolin-3-yl]-ethanone;  
 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-ethanone;

1-(2,6-Dimethyl-4-phenyl-quinolin-3-yl)-ethanone; and  
1-(2-Methyl-4-phenyl-6-trifluoromethoxy-quinolin-3-yl)-ethanone.

The six compounds excluded from the scope for formula I are known from chemical libraries. Said six compounds were never disclosed in relation with GABA<sub>B</sub> receptors.

The compounds of formula I and their salts are distinguished by valuable therapeutic properties. It has been found that the compounds are active on the GABA<sub>B</sub> receptor.

$\gamma$ -Aminobutyric acid (GABA), the most abundant inhibitory neurotransmitter, activates both ionotropic GABA<sub>A/C</sub> and metabotropic GABA<sub>B</sub> receptors (*Hill and Bowery, Nature, 290, 149-152, 1981*). GABA<sub>B</sub> receptors that are present in most regions of the mammalian brain on presynaptic terminals and postsynaptic neurons are involved in the fine-tuning of inhibitory synaptic transmission. Presynaptic GABA<sub>B</sub> receptors through modulation of high-voltage activated Ca<sup>2+</sup> channels (P/Q- and N-type) inhibit the release of many neurotransmitters. Postsynaptic GABA<sub>B</sub> receptors activates G-protein coupled inwardly rectifying K<sup>+</sup> (GIRK) channel and regulates adenylyl cyclase (*Billinton et al., Trends Neurosci., 24, 277-282, 2001; Bowery et al., Pharmacol. Rev., 54, 247-264, 2002*). Because the GABA<sub>B</sub> receptors are strategically located to modulate the activity of various neurotransmitter systems, GABA<sub>B</sub> receptor ligands hence could have potential therapeutics in the treatment of anxiety, depression, epilepsy, schizophrenia and cognitive disorders (*Vacher and Bettler, Curr. Drug Target, CNS Neurol. Disord., 2, 248-259, 2003; Bettler et al., Physiol Rev. 84, 835-867, 2004*).

Native GABA<sub>B</sub> receptors are heteromeric structures composed of two types of subunits, GABA<sub>B</sub>R1 and GABA<sub>B</sub>R2 subunits (*Kaupmann et al., Nature, 386, 239-246, 1997 and Nature, 396, 683-687, 1998*). The structure of GABA<sub>B</sub>R1 and R2 show that they belong to a family of G-protein coupled receptors (GPCRs) called family 3. Other members of the family 3 GPCRs include the metabotropic glutamate (mGlu1-8), Calcium-sensing, vomeronasal, pheromone and putative taste receptors (*Pin et al., Pharmacol. Ther. 98, 325-354, 2003*). The family 3 receptors (including GABA<sub>B</sub> receptors) are characterized by two distinctly separated topological domains: an exceptionally long extracellular amino-terminal domain (ATD, 500-600 amino acids), which contains a venus flytrap module for the agonist binding (orthosteric site) (*Galvez et al., J. Biol. Chem., 275, 41166-41174, 2000*) and the 7TM helical segments plus intracellular carboxyl-terminal domain that is involved in receptor activation and G-protein coupling. The

mechanism of receptor activation by agonist in GABA<sub>B</sub>R1R2 heterodimer is unique among the GPCRs. In the heteromer, only GABA<sub>B</sub>R1 subunit binds to GABA, while the GABA<sub>B</sub>R2 is responsible for coupling and activation of G-protein (*Havlickova et al., Mol. Pharmacol.* 62, 343-350, 2002; *Kniazeff et al., J. Neurosci.*, 22, 7352-7361, 2002).

5        *Schuler et al., Neuron*, 31, 47-58, 2001 have demonstrated that the GABA<sub>B</sub>R1 knock-out (KO) mice exhibit spontaneous seizures and hyperalgesia. These KO mice have lost all the biochemical and electrophysiological GABA<sub>B</sub> responses. Interestingly, the GABA<sub>B</sub>R1 KO mice were more anxious in two anxiety paradigm, namely the light-dark box (decreased time in light) and staircase tests (decreased rears and steps climbed). They  
10 showed a clear impairment of passive avoidance performance model indicating impaired memory processes. The GABA<sub>B</sub>R1 KO also displayed increased hyperlocomotion and hyperactivity in new environment. The GABA<sub>B</sub>R1 gene is mapped to chromosome 6p21.3, which is within the HLA class I, a region with linkage for schizophrenia, epilepsy and dyslexia (*Peters et al., Neurogenetics*, 2, 47-54, 1998). *Mondabon et al., Am. J. Med. Genet* 122B/1, 134, 2003 have reported about a weak association of the Ala20Val polymorphism of GABA<sub>B</sub>R1 gene with schizophrenia. Moreover, *Gassmann et al., J. Neurosci.* 24, 6086-6097, 2004 has shown that GABA<sub>B</sub>R2KO mice suffer from spontaneous seizures, hyperalgesia, hyperlocomotor activity and severe memory impairment, comparable to GABA<sub>B</sub>R1KO mice. Therefore, heteromeric GABA<sub>B</sub> R1R2 receptors are  
15 responsible for these phenotypes.  
20

Baclofen (Lioresal<sup>®</sup>,  $\beta$ -chlorophenyl GABA), a selective GABA<sub>B</sub> receptor agonist with EC<sub>50</sub> = 210 nM at native receptor, is the only ligand, which has been used since 1972 in clinical study for the treatment of spasticity and skeletal muscle rigidity in patients following spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, cerebral  
25 palsy. Most of the preclinical and clinical studies conducted with baclofen and GABA<sub>B</sub> receptor agonists were for the treatment of neuropathic pain and craving associated with cocaine and nicotine (*Misgeld et al., Prog. Neurobiol.* 46, 423-462, 1995; *Enna et al., Life Sci*, 62, 1525-1530, 1998; *McCarson and Enna, Neuropharmacology*, 38, 1767-1773, 1999; *Brebner et al., Neuropharmacology*, 38, 1797-1804, 1999; *Paterson et al., Psychopharmacology*, 172, 179-186, 2003). In panic disorder patients, Baclofen was shown to be significantly effective in reducing the number of panic attacks and symptoms of anxiety as assessed with the Hamilton anxiety scale, Zung anxiety scale and Katz-R nervousness subscale (*Breslow et al., Am. J. Psychiatry*, 146, 353-356, 1989). In a study with a small group of veterans with chronic, combat-related posttraumatic stress disorder  
30 (PTSD), baclofen was found to be an effective and well-tolerated treatment. It resulted in  
35

significant improvements in the overall symptoms of PTSD, most notably the avoidance, emotional numbing and hyperarousal symptoms and also in reduced accompanying anxiety and depression (*Drake et al., Ann. Pharmacother.* 37., 1177-1181, 2003). In preclinical study, baclofen was able to reverse the reduction in prepulse inhibition (PPI) of the acoustic startle response induced by dizocilpine, but not by apomorphine in rat PPI model of psychosis (*Bortolato et al., Psychopharmacology*, 171, 322-330, 2004). Therefore, GABA<sub>B</sub> receptor agonist has a potential in the pharmacological therapy of psychotic disorders. Unfortunately, Baclofen has a number of side-effects including the poor blood-brain-barrier penetration, very short duration of action and narrow therapeutic window (muscle relaxation, sedation and tolerance) that limit its utility.

*Urwyler et al., Mol. Pharmacol.*, 60, 963-971, 2001 have reported on a novel class of GABA<sub>B</sub> receptor ligands, called positive allosteric modulators, CGP7930 [2,6-di-tert-butyl-4-(3-hydroxy-2,2-dimethyl-propyl)-phenol] and its aldehyde analogue CGP13501. These ligands have no effect on their own at GABA<sub>B</sub> receptors, but in concert with endogenous GABA, they increase both the potency and maximal efficacy of GABA at the GABA<sub>B</sub>R1R2 (*Pin et al., Mol. Pharmacol.*, 60, 881-884, 2001). Interestingly, recent study with CGP7930 (*Binet et al., J Biol Chem.*, 279, 29085-29091, 2004) has shown that this positive modulator activates directly the seven transmembrane domains (7TMD) of GABA<sub>B</sub>R2 subunit. *Mombereau et al., Neuropsychopharmacology*, 1-13, 2004 have recently reported on the anxiolytic effects of acute and chronic treatment with the GABA<sub>B</sub> receptor positive modulator, GS39783 (*N,N*-dicyclopentyl-2-methylsulfanyl-5-nitro-pyrimidine-4,6-diamine) (*Urwyler et al., J. Pharmacol. Exp. Ther.*, 307, 322-330, 2003) in the light-dark box and elevated zero maze test models of anxiety. No tolerance after chronic treatment (21 days) with GS39783 (10 mg/kg, P.O., once daily) was observed. Because the GABA<sub>B</sub> enhancers have no effect on receptor activity in the absence of GABA, but do enhance allosterically the affinity of the GABA<sub>B</sub> receptor for the endogenous GABA, it is expected that these ligands should have an improved side effect profile as compared to baclofen. Indeed, GS39783 at 0.1-200 mg/kg, PO had no effect on spontaneous locomotor activity, rotarod, body temperature and traction test in comparison to baclofen, which showed these side effects at 2.5-15 mg/kg, PO. GS39783 did not have any effect on cognition performance as assessed by passive avoidance behavioral test in mice and rats. Furthermore, GS39783 exhibited anxiolytic-like effects in the elevated plus maze (rat), elevated zero maze (mice and rats), and the stress-induced hyperthermia (mice) test paradigms. Therefore, GS39783 represents a novel anxiolytic without side-effects associated with baclofen or benzodiazepines (*Cryan et al., J Pharmacol Exp Ther.*, 310, 952-963, 2004). The preclinical investigation with the CGP7930

and GS39783 has shown that both compounds were effective at decreasing cocaine self-administration in rats (*Smith et al., Psychopharmacology, 173, 105-111, 2004*). The positive modulator, CGP7930 has also been preclinically studied for the treatment of Gastro-Esophageal Reflux Disease (GERD) and was found to be effective (WO 03/090731, Use of  
5 GABA<sub>B</sub> receptor positive modulators in gastro-intestinal disorders).

Positive allosteric modulators have been reported for other family 3 GPCRs including mGlu1 receptor (*Knoflach et al., Proc. Natl. Acad. Sci., USA, 98, 13402-13407, 2001; Wichmann et al., Farmaco, 57, 989-992, 2002*), Calcium-sensing receptor (NPS R-467 and NPS R-568) (*Hammerland et al., Mol. Pharmacol., 53, 1083-1088, 1998*) (US  
10 6,313, 146), mGlu2 receptor [LY487379, *N*-(4-(2-methoxyphenoxy)-phenyl)-*N*-(2,2,2-trifluoroethylsulfonyl)-pyrid-3-yl)methylamine and its analogs] (WO 01/56990, Potentiators of glutamate receptors) and mGlu5 receptor (CPPHA, *N*-{4-chloro-2-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl] phenyl}-2-hydroxybenzamide) (*O'Brien et al., J. Pharmacol. Exp. Ther., 27, Jan. 27, 2004*). Interestingly, it has been demonstrated that  
15 these positive modulators bind to a novel allosteric site located within the 7TMD region, thereby enhancing the agonist affinity by stabilizing the active state of the 7TMD region (*Knoflach et al., Proc. Natl. Acad. Sci., USA 98, 13402-13407, 2001; Schaffhauser et al., Mol. Pharmacol., 64, 798-810, 2003*). Moreover, the NPS R-467, NPS R-568 (Tecalset) and related compounds represent the first positive allosteric modulators that entered the  
20 clinical trials due to their allosteric mode of action.

Objects of the invention are the compounds of formula I and pharmaceutically acceptable acid addition salts thereof, the preparation of the compounds of formula I and salts thereof, medicaments containing a compound of formula I or a pharmaceutically acceptable acid addition salts thereof.

25 A further object of the invention is the use of the compound of formula I or of a compound selected from the group consisting of:  
1-(6-Chloro-2-methyl-4-phenyl-quinolin-3-yl)-ethanone;  
1-(6-Bromo-4-phenyl-2-piperidin-1-yl-quinolin-3-yl)-ethanone;  
1-[4-(4-Chloro-phenyl)-2-methyl-quinolin-3-yl]-ethanone;  
30 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-ethanone;  
1-(2,6-Dimethyl-4-phenyl-quinolin-3-yl)-ethanone; and  
1-(2-Methyl-4-phenyl-6-trifluoromethoxy-quinolin-3-yl)-ethanone,  
and acceptable acid addition salts thereof for the manufacture of such medicaments useful in the control or prevention of illnesses, especially of illnesses and disorders of the  
35 kind referred to earlier, such as anxiety, depression, epilepsy, schizophrenia, cognitive

disorders, spasticity and skeletal muscle rigidity, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, cerebral palsy, neuropathic pain and craving associated with cocaine and nicotine, psychosis, panic disorder, posttraumatic stress disorders or gastrointestinal disorders, and, respectively, for the manufacture of corresponding  
5 medicaments.

The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination.

As used herein, the term "Aryl" means a monovalent cyclic aromatic hydrocarbon moiety. Preferred aryls include, but are not limited to, optionally substituted phenyl or  
10 naphthyl, as well as those aryl groups specifically illustrated by the examples herein below. Examples of substituents for aryl groups are hydroxy, halo, C<sub>1</sub>-C<sub>7</sub> alkyl, C<sub>1</sub>-C<sub>7</sub> haloalkyl, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> haloalkoxy, C<sub>1</sub>-C<sub>7</sub> alkoxyalkyl, C<sub>1</sub>-C<sub>7</sub> alkylsulfonyl, di(C<sub>1</sub>-C<sub>7</sub>)alkylamino or C<sub>3</sub>-C<sub>8</sub> cycloalkyl.

"aryloxy" denotes an aryl group wherein the aryl group is as defined above and the  
15 aryl group is connected via an oxygen atom. Preferred aryloxy is PhO-.

"C<sub>1</sub>-C<sub>7</sub> alkyl" denotes a straight- or branched-carbon chain group containing from 1 to 7 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, pentyl, n-hexyl as well as those specifically illustrated by the examples herein below.

"C<sub>1</sub>-C<sub>7</sub> haloalkyl" denotes a C<sub>1</sub>-C<sub>7</sub> alkyl group as defined above which is substituted  
20 by one or more halogen. Examples of C<sub>1</sub>-C<sub>7</sub> haloalkyl include but are not limited to methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, pentyl or n-hexyl substituted by one or more Cl, F, Br or I atom(s) as well as those groups specifically illustrated by the examples herein below. Preferred C<sub>1</sub>-C<sub>7</sub> haloalkyl are difluoro- or  
25 trifluoro-methyl or ethyl.

"C<sub>1</sub>-C<sub>7</sub> alkoxy" denotes a group wherein the alkyl group is as defined above and the alkyl group is connected via an oxygen atom. Preferred alkoxy are MeO- and Et-O as well as those groups specifically illustrated by the examples herein below.

"C<sub>1</sub>-C<sub>7</sub> haloalkoxy" denotes a C<sub>1</sub>-C<sub>7</sub> alkoxy group as defined above which is  
30 substituted by one or more halogen. Examples of C<sub>1</sub>-C<sub>7</sub> haloalkoxy include but are not limited to methoxy or ethoxy, substituted by one or more Cl, F, Br or I atom(s) as well as those groups specifically illustrated by the examples herein below. Preferred C<sub>1</sub>-C<sub>7</sub> haloalkoxy are difluoro- or trifluoro-methoxy or ethoxy.

“Halogen” denotes chlorine, iodine, fluorine and bromine.

“C<sub>1</sub>-C<sub>7</sub> alkoxyalkyl” denotes a C<sub>1</sub>-C<sub>7</sub> alkyl group as defined herein above which is substituted by a C<sub>1</sub>-C<sub>7</sub> alkoxy group as defined herein above.

“C<sub>1</sub>-C<sub>7</sub> alkylsulfonyl” denotes a sulfonyl group which is substituted by a C<sub>1</sub>-C<sub>7</sub> alkyl group as defined herein above. Examples of C<sub>1</sub>-C<sub>7</sub> alkylsulfonyl include but are not limited to methylsulfonyl and ethylsulfonyl as well as those groups specifically illustrated by the examples herein below.

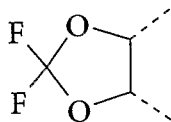
“di(C<sub>1</sub>-C<sub>7</sub>)alkylamino” denotes a -NR<sup>7</sup>R<sup>8</sup> group, wherein R<sup>7</sup> and R<sup>8</sup> are C<sub>1</sub>-C<sub>7</sub> alkyl groups as defined herein above. Examples of di(C<sub>1</sub>-C<sub>7</sub>)alkylamino groups include but are not limited to di(methyl)amino, di(ethyl)amino, methylethylamino, as well as those groups specifically illustrated by the examples herein below.

“Hydroxy” denotes a -OH group.

“C<sub>3</sub>-C<sub>8</sub> cycloalkyl” denotes a saturated carbon cyclic ring having 3 to 8 carbon atoms as ring members and includes but is not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, as well as those groups specifically illustrated by the examples herein below.

“4 to 8 membered heterocycloalkyl” denote a saturated mono- or bi-cyclic ring comprising from 1 to 7 carbon atoms as ring members, the other remaining ring member atoms being selected from one or more O, N and S. Preferred 4 to 8 membered heterocycloalkyl groups are 5 or 6 membered heterocycloalkyl groups. Examples of 4 to 8 and 5 or 6 membered heterocycloalkyl groups include but are not limited to optionally substituted azetidiny, piperidiny, piperaziny, homopiperaziny, azepiny, pyrrolidiny, pyrazolidiny, imidazolidiny, imidazolidiny, pyridiny, pyridaziny, pyrimidiny, oxazolidiny, isoxazolidiny, morpholiny, thiazolidiny, isothiazolidiny, quinuclidiny, quinoliny, isoquinoliny, benzimidazolyl, thiadiazolylidiny, benzothiazolidiny, benzoazolylidiny, dihydrofuryl, tetrahydrofuryl, dihydropyrany, tetrahydropyrany, thiomorpholiny, thiomorpholiny sulfoxide, thiomorpholiny sulfone, dihydroquinoliny, dihydroisoquinoliny, tetrahydroquinoliny, tetrahydroisoquinoliny, 1-oxo-thiomorpholin, 1,1-dioxo-thiomorpholin, 1,4-diazepane, 1,4-oxazepane and 8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl, as well as those groups specifically illustrated by the examples herein below.

“R<sup>6</sup> together with R<sup>5</sup> form a 5 or 6 membered heterocycloalkyl group” denotes 5 or 6 membered heterocycloalkyl groups as defined above which is fused to the quinoline group via R<sup>5</sup> and R<sup>6</sup>. An example of such group is but is not limited to the following group:



5

The term “pharmaceutically acceptable acid addition salts” embraces salts with inorganic and organic acids, which include but are not limited to hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid.

10 Preferred groups for R<sup>1</sup> may be selected from the group consisting of methyl, ethyl, propyl, i-propyl, butyl, i-butyl, and t-butyl.

Preferred groups for R<sup>2</sup> may be selected from the group consisting of methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, CHF<sub>2</sub> and CF<sub>3</sub>.

15 Preferred groups for R<sup>3</sup> may be selected from the group consisting of hydrogen, Cl and F.

Preferred groups for R<sup>4</sup> may be selected from the group consisting of hydrogen, methoxy, methylsulfonyl, Cl and F.

20 Preferred groups for R<sup>5</sup> may be selected from the group consisting of Br, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, and t-butyl, CF<sub>3</sub>O, PhO, methoxy, methylsulfonyl, Cl, F or I, and when R<sup>5</sup> is -NR<sup>7</sup>R<sup>8</sup>, R<sup>7</sup> and R<sup>8</sup> together with the nitrogen atom to which they are attached may form a group selected from the group consisting of piperidin-1-yl, morpholin-4-yl, pyrrolidin-1-yl, piperazin-1-yl, pyrrolidin-1-yl, azetidine-1-yl, and azepan-1-yl, which may be substituted by one or more F, methyl, ethyl, propyl, i-propyl, 25 butyl, i-butyl, t-butyl, hydroxy, methoxy, phenyl, dimethylamino and 1,4-oxazepane and 8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl.

More preferred groups for R<sup>5</sup> may be selected from the group consisting of Br, I, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, and t-butyl, CF<sub>3</sub>O, PhO, methoxy, methylsulfonyl, Cl or F, and when R<sup>5</sup> is -NR<sup>7</sup>R<sup>8</sup>, R<sup>7</sup> and R<sup>8</sup> together with the nitrogen

atom to which they are attached may form a group selected from the group consisting of piperidin-1-yl, 3,3-difluoro-piperidin-1-yl, 4-hydroxy-4-methyl-piperidin-1-yl, 4-methoxy-piperidine-1-yl, morpholin-4-yl, pyrrolidin-1-yl, 2-methyl-pyrrolidin-1-yl, 4-methyl-piperazin-1-yl, 3-hydroxy-pyrrolidin-1-yl, 3-hydroxy-azetidine-1-yl, 4-hydroxy-4-phenyl-piperidin-1-yl, 3,3-dimethylamine-pyrrolidin-1-yl, azepan-1-yl and 1,4-oxazepane and 8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl.

Preferred compounds of the invention are those compounds of formula I, wherein

- R<sup>1</sup> is C<sub>1</sub>-C<sub>7</sub> alkyl;
- R<sup>2</sup> is C<sub>1</sub>-C<sub>7</sub> alkyl, phenyl, C<sub>1</sub>-C<sub>7</sub> haloalkyl or C<sub>3</sub>-C<sub>8</sub> cycloalkyl;
- 10 R<sup>3</sup>, R<sup>4</sup> are each independently hydrogen, halo, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> alkylsulfonyl;
- R<sup>5</sup> is halo, C<sub>1</sub>-C<sub>7</sub> haloalkoxy, aryloxy,  
or is -NR<sup>7</sup>R<sup>8</sup> wherein R<sup>7</sup> and R<sup>8</sup> are C<sub>1</sub>-C<sub>7</sub> alkyl, or R<sup>7</sup> and R<sup>8</sup> may, together with  
the nitrogen atom to which they are attached, form a 4 to 8 membered  
heterocycloalkyl group which may be substituted by one or more substituent(s)  
15 selected from the group consisting of halo, C<sub>1</sub>-C<sub>7</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>7</sub> alkoxy,  
phenyl and di(C<sub>1</sub>-C<sub>7</sub>)alkylamino;
- R<sup>6</sup> is hydrogen or together with R<sup>5</sup> may form a 5 or 6 membered heterocycloalkyl  
group which may be substituted by one or more halogen.

Also preferred compounds of the invention are those compounds of formula I  
20 wherein R<sup>2</sup> is C<sub>1</sub>-C<sub>7</sub> alkyl, for example the following compounds:

- 1-(6-Bromo-2-ethyl-4-phenyl-quinolin-3-yl)-propan-1-one;
- 1-(6-Bromo-2-isobutyl-4-phenyl-quinolin-3-yl)-ethanone;
- 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-3-methyl-butan-1-one;
- 1-[4-(4-Chloro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-ethanone;
- 25 1-(6-Bromo-2-isopropyl-4-phenyl-quinolin-3-yl)-2-methyl-propan-1-one;
- 1-[4-(3,4-Dichloro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-ethanone;
- 1-[4-(4-Chloro-phenyl)-2-methyl-6-phenoxy-quinolin-3-yl]-ethanone; and
- 1-[4-(3-Chloro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-ethanone.

Other preferred are those compounds of formula I wherein, wherein R<sup>2</sup> is C<sub>1</sub>-C<sub>7</sub>  
30 haloalkyl, for example the following compounds:

- 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-2,2,2-trifluoro-ethanone;
- 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-2,2-difluoro-ethanone;
- 2,2,2-Trifluoro-1-(2-methyl-4-phenyl-6-trifluoromethoxy-quinolin-3-yl)-ethanone;

- 1-[4-(3-Chloro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-2,2,2-trifluoro-ethanone;
- 1-[4-(4-Chloro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-2,2,2-trifluoro-ethanone;
- 5 2,2,2-Trifluoro-1-[4-(4-methoxy-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-ethanone;
- 2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-ethanone;
- 1-(6-tert-Butyl-2-methyl-4-phenyl-quinolin-3-yl)-2,2,2-trifluoro-ethanone;
- 10 1-(2,2-Difluoro-6-methyl-8-phenyl-[1,3]dioxolo[4,5-g]quinolin-7-yl)-2,2,2-trifluoro-ethanone;
- 1-[4-(3,4-Difluoro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-2,2,2-trifluoro-ethanone;
- 2,2,2-Trifluoro-1-[4-(4-methanesulfonyl-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-ethanone;
- 15 2,2,2-Trifluoro-1-[4-(3-fluoro-4-methoxy-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-ethanone;
- 2,2,2-Trifluoro-1-(2-methyl-4-phenyl-6-piperidin-1-yl-quinolin-3-yl)-ethanone;
- 2,2,2-Trifluoro-1-(2-methyl-6-morpholin-4-yl-4-phenyl-quinolin-3-yl)-ethanone;
- 20 2,2,2-Trifluoro-1-(2-methyl-4-phenyl-6-pyrrolidin-1-yl-quinolin-3-yl)-ethanone;
- 2,2,2-Trifluoro-1-[2-methyl-6-(2-methyl-pyrrolidin-1-yl)-4-phenyl-quinolin-3-yl]-ethanone;
- 2,2,2-Trifluoro-1-[2-methyl-6-(4-methyl-piperazin-1-yl)-4-phenyl-quinolin-3-yl]-ethanone;
- 25 2,2,2-Trifluoro-1-[6-(3-hydroxy-pyrrolidin-1-yl)-2-methyl-4-phenyl-quinolin-3-yl]-ethanone;
- 2,2,2-Trifluoro-1-[6-(3-hydroxy-azetidin-1-yl)-2-methyl-4-phenyl-quinolin-3-yl]-ethanone;
- 1-[6-Bromo-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone;
- 30 1-[6-Bromo-4-(4-fluoro-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone;
- 2,2,2-Trifluoro-1-[4-(4-methanesulfonyl-phenyl)-2-methyl-6-piperidin-1-yl-quinolin-3-yl]-ethanone;
- 2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-2-methyl-6-piperidin-1-yl-quinolin-3-yl]-ethanone;
- 35 2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-2-methyl-6-morpholin-4-yl-quinolin-3-yl]-ethanone;

- 2,2,2-Trifluoro-1-[4-(4-methanesulfonyl-phenyl)-2-methyl-6-pyrrolidin-1-yl-quinolin-3-yl]-ethanone;
- 2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-2-methyl-6-pyrrolidin-1-yl-quinolin-3-yl]-ethanone;
- 5 2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-6-(3-hydroxy-pyrrolidin-1-yl)-2-methyl-quinolin-3-yl]-ethanone;
- 2,2,2-Trifluoro-1-[6-(4-hydroxy-4-phenyl-piperidin-1-yl)-2-methyl-4-phenyl-quinolin-3-yl]-ethanone;
- 2,2,2-Trifluoro-1-[6-(4-hydroxy-4-phenyl-piperidin-1-yl)-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-ethanone;
- 10 2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-6-(4-hydroxy-4-phenyl-piperidin-1-yl)-2-methyl-quinolin-3-yl]-ethanone;
- 2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-6-(3-hydroxy-azetidin-1-yl)-2-methyl-quinolin-3-yl]-ethanone;
- 15 1-[6-Azepan-1-yl-4-(4-fluoro-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone;
- 1-(6-Azepan-1-yl-2-methyl-4-phenyl-quinolin-3-yl)-2,2,2-trifluoro-ethanone;
- 1-[6-(3-Dimethylamino-pyrrolidin-1-yl)-2-methyl-4-phenyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone;
- 1-[6-(3-Dimethylamino-pyrrolidin-1-yl)-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone;
- 20 1-[6-(3-Dimethylamino-pyrrolidin-1-yl)-4-(4-fluoro-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone;
- 2,2,2-Trifluoro-1-[6-iodo-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-ethanone;
- 25 2,2,2-Trifluoro-1-[6-(4-hydroxy-4-methyl-piperidin-1-yl)-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-ethanone;
- 2,2,2-Trifluoro-1-[4-(4-methanesulfonyl-phenyl)-6-(4-methoxy-piperidin-1-yl)-2-methyl-quinolin-3-yl]-ethanone;
- 1-[6-(3,3-Difluoro-piperidin-1-yl)-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone; and
- 30 2,2,2-Trifluoro-1-[4-(4-methanesulfonyl-phenyl)-2-methyl-6-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-quinolin-3-yl]-ethanone.

Still other preferred compounds of the invention are those compounds of formula I, wherein R<sup>2</sup> is C<sub>3</sub>-C<sub>8</sub> cycloalkyl, for example the following compounds:

[6-Bromo-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-cyclopropyl-methanone;

Cyclopropyl-[4-(4-methanesulfonyl-phenyl)-2-methyl-6-morpholin-4-yl-quinolin-3-yl]-methanone;

5 Cyclopropyl-[4-(4-methanesulfonyl-phenyl)-2-methyl-6-piperidin-1-yl-quinolin-3-yl]-methanone;

[(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-cyclopropyl-methanone;

[6-Bromo-4-(4-fluoro-phenyl)-2-methyl-quinolin-3-yl]-cyclopropyl-methanone;

Cyclopropyl-(2-methyl-4-phenyl-6-piperidin-1-yl-quinolin-3-yl)-methanone; and

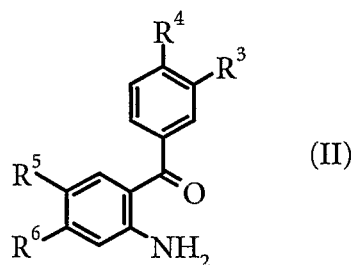
10 Cyclopropyl-(2-methyl-6-morpholin-4-yl-4-phenyl-quinolin-3-yl)-methanone.

Still other preferred compounds of the invention are those compounds of formula I, wherein R<sup>2</sup> is phenyl, for example the following compounds:

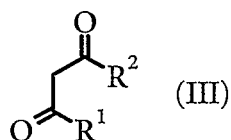
(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-phenyl-methanone; and

[4-(3-Chloro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-phenyl-methanone.

15 The afore-mentioned compounds of formula I can be manufactured by the following process of the invention comprising the step of reacting a compound of formula II



with a compound of formula III



20

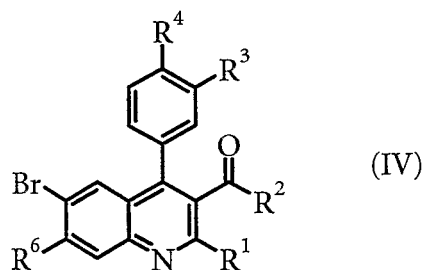
wherein R<sup>1</sup> to R<sup>6</sup> are as defined in formula I.

to give the compound of formula I;

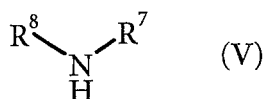
and if desired, converting the compound of formula I obtained into a pharmaceutically acceptable acid addition salt.

25

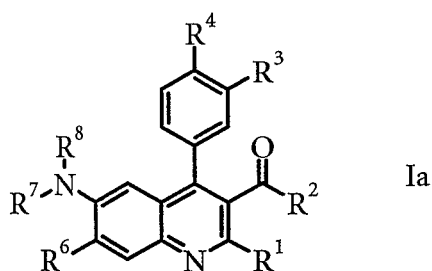
The afore-mentioned compounds of formula I can also be manufactured in accordance with the invention by the following variant process comprising the step of reacting a compound of formula IV



with a compound of formula V



to give the compound of formula Ia;



wherein  $R^1$  to  $R^8$  are as defined in formula I;

and if desired, converting the compound of formula Ia obtained into a pharmaceutically acceptable acid addition salt. It is understood that the compounds of formula Ia correspond to the compounds of formula I wherein  $R^5$  is  $-NR^7R^8$  and  $R^7$  and  $R^8$  are as defined for formula I.

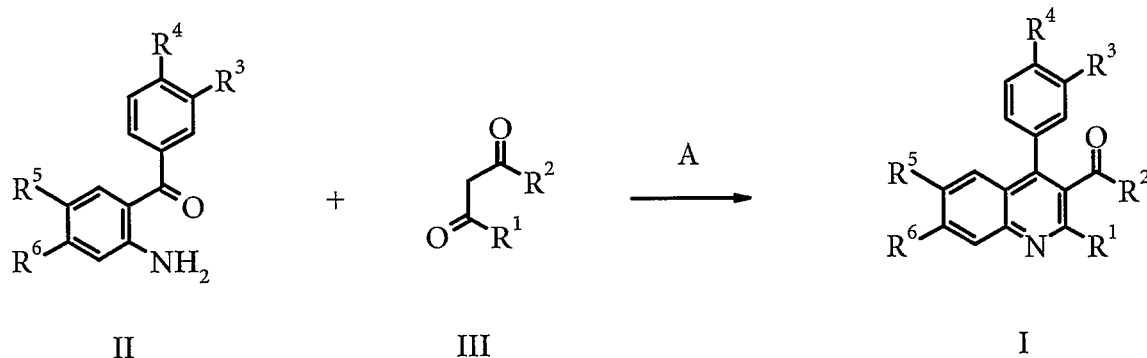
The invention also encompasses a compound of formula I or Ia, whenever it is prepared according to the above-mentioned processes.

In the following the preparation of compounds of formula I is described in more detail:

In schemes 1 and 2 are described processes for preparation of compound of formula I or Ia.

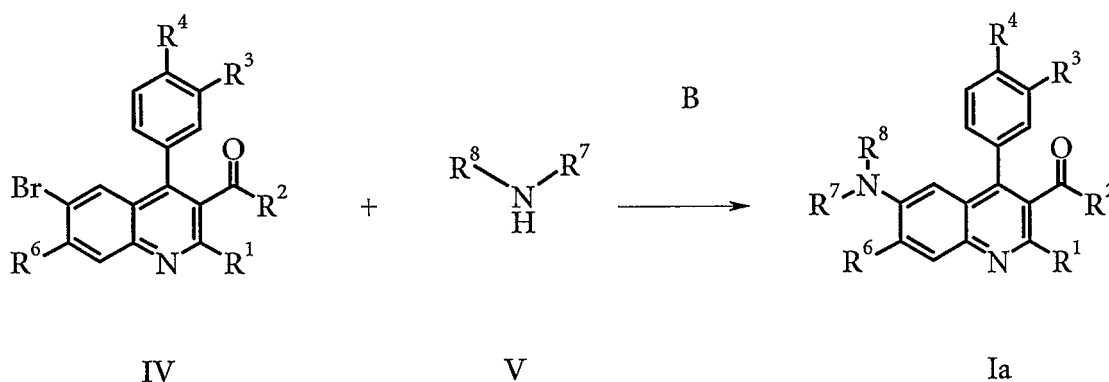
The preparation of compounds of formula I are further described in detail in working examples 1 - 46.

Scheme 1

A) cat. (NaAuCl<sub>4</sub> 2H<sub>2</sub>O)Method A

According to the procedure developed by A. Arcadi, M. Chiarini, S. Di Giuseppe,  
 5 and F. Marinelli, Synlett 203-206 (2003), the 2-aminobenzophenone II is reacted with the  
 1,3-dione III and sodium tetrachloroaurate(III) dihydrate as catalysator. The residue can  
 be purified by conventional methods.

Scheme 2

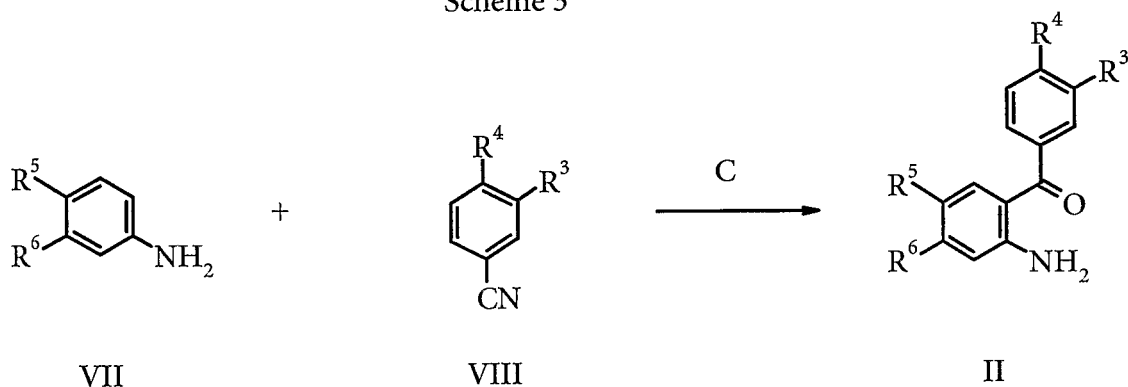
B) cat. Pd<sub>2</sub>dba<sub>3</sub> CHCl<sub>3</sub>, rac-BINAP, Cs<sub>2</sub>CO<sub>3</sub>Method B

Following a methodology developed by J. P. Wolfe and S. L. Buchwald (J. Org.  
 10 Chem. 2000, 65, 1144-1157) tris(dibenzylideneacetone)dipalladium chloroform complex  
 is added to rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, cesium carbonate, the 2-  
 amino-4-bromo-benzoquinone IV, and the amine V. The residue can be purified by  
 conventional methods.

15 One part of the starting material used in the general procedures of schemes 1 and 2  
 is commercially available (e.g. some of the benzophenones of formula IV, all 1,3-

diketones of formula III, and all the amines of formula V). However the non commercially available part of said starting material can be prepared according to the general procedure of method C for compounds of formula II as outlined hereafter in scheme 3, or according to the general procedure of method A for providing suitable  
 5 compounds of formula IV as outline hereinabove in scheme 1. Unless otherwise specified, the intermediate compounds described therein are novel compounds:

Scheme 3



C) BCl<sub>3</sub>, GaCl<sub>3</sub>

#### Method C

Following a procedure developed by T. Sugawara, T. Toyoda, M. Adachi, and K. Sasakura, J. Am. Chem. Soc. 100, 4842-4852 (1978) and improved by A. W. Douglas, N. L. Abramson, I. N. Houpis, S. Karady, A. Molina, L. C. Xavier, N. Yasuda, Tetrahedron Lett. 35, 6807-6810 (1994), either gallium (III) chloride or aluminium (III) chloride are mixed with a chlorinated solvent. Aniline VII, boron trichloride and benzonitrile VIII are then added to the cold mixture. The crude product can be purified by conventional  
 15 methods.

The preparation of compounds of formula II is further described in detail in working examples A1 to A16.

As mentioned earlier, the compounds of formula I and their pharmaceutically acceptable addition salts possess valuable pharmacological properties. It has been found  
 20 that the compounds of the present invention have an affinity to the GABA<sub>B</sub> receptor.

The compounds were investigated in accordance with the tests given hereinafter.

#### Intracellular Ca<sup>2+</sup> mobilization assay

The Chinese Hamster Ovary (CHO) cells stably expressing human GABA<sub>B</sub>R1aR2a and Gα16 were seeded at 5x10<sup>4</sup> cells/well in the poly-D-lysine treated, 96-well,

black/clear-bottomed plates (BD Biosciences, Palo Alto, CA). 24 h later, the cells were loaded for 90 min at 37°C with 4  $\mu$ M Flou-4 acetoxymethyl ester (Catalog No. F-14202, Molecular Probes, Eugene, OR) in loading buffer (1xHBSS, 20 mM HEPES, 2.5 mM Probenecid). Hanks' Balanced Salt Solution (HBSS) (10X) (catalog No. 14065-049) and

5 HEPES (1M) (catalog No. 15630-056) were purchased from Invitrogen, Carlsbad, CA. Probenecid (250 mM) (catalog No. P8761) was from Sigma, Buchs, Switzerland. The cells were washed five times with loading buffer to remove excess dye and intracellular calcium mobilization,  $[Ca^{2+}]_i$  were measured using a Fluorometric Imaging Plate Reader (FLIPR, Molecular Devices, Menlo Park, CA) as described previously (Porter et al., Br. J.

10 Pharmacol., 128, 13-20, 1999). The enhancers were applied 15 min before the application of the GABA. For GABA shift assay, concentration-response curves of GABA (0.0003-30  $\mu$ M) were determined in the absence and presence of 10  $\mu$ M enhancer. The GABA-shift is defined as  $\text{Log} [EC_{50} (\text{GABA} + 10 \mu\text{M enhancer}) / EC_{50} (\text{GABA alone})]$ . The % maximum

15 enhancing effect (%  $E_{\text{max}}$ ) and potency ( $EC_{50}$  value) of each enhancer was determined from concentration-response curve of the enhancer (0.001-30  $\mu$ M) in the presence of 10 nM GABA ( $EC_{10}$ ). Responses were measured as peak increase in fluorescence minus basal, normalized to the maximal stimulatory effect induced by 10  $\mu$ M GABA alone (considered 100%) and 10 nM GABA alone (considered 0%). The data were fitted with

20 the equation  $Y = 100 + (Max - 100) / (1 + (EC_{50} / [drug])^n)$  where Max is the maximum effect,  $EC_{50}$  the concentration eliciting a half-maximum effect and n the Hill slope.

| Example | Intracellular $Ca^{2+}$ mobilization Assay in<br>CHO-GABA <sub>B</sub> R1aR2a-G $\alpha$ 16 cell |                                      | GABA shift                                                                           |
|---------|--------------------------------------------------------------------------------------------------|--------------------------------------|--------------------------------------------------------------------------------------|
|         | $E_{\text{max}}$ (%) at<br>10 nM GABA alone = 0%<br>10 $\mu$ M GABA alone = 100%                 | $EC_{50}$ ( $\mu$ M) at<br>10nM GABA | $\text{Log} [EC_{50}(\text{GABA} + 10 \mu\text{M cp}) / EC_{50}(\text{GABA alone})]$ |
| 3       | 124                                                                                              | 0.80                                 | -1.20                                                                                |
| 11      | 65                                                                                               | 0.80                                 | -1.00                                                                                |
| 15      | 67                                                                                               | 1.60                                 | -1.15                                                                                |
| 19      | 63                                                                                               | 0.90                                 | -0.70                                                                                |
| 33      | 62                                                                                               | 0.33                                 | -0.90                                                                                |

|    |    |      |       |
|----|----|------|-------|
| 56 | 58 | 2.20 | -0.90 |
|----|----|------|-------|

The compounds of formula I as well as their pharmaceutically usable acid addition salts can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and their pharmaceutically usable acid addition salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragees and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients e.g. for tablets, dragées and hard gelatine capsules.

Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols.

Suitable excipients for the manufacture of solutions and syrups include but are not limited to water, polyols, saccharose, invert sugar, glucose.

Suitable excipients for injection solutions include but are not limited to water, alcohols, polyols, glycerol, vegetable oils.

Suitable excipients for suppositories include but are not limited to natural or hardened oils, waxes, fats, semi-liquid or liquid polyols.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of general formula I should be appropriate, although the above upper limit can also be exceeded when necessary.

Tablet Formulation (Wet Granulation)

| <u>Item</u> | <u>Ingredients</u>            | <u>mg/tablet</u> |       |        |        |
|-------------|-------------------------------|------------------|-------|--------|--------|
|             |                               | 5 mg             | 25 mg | 100 mg | 500 mg |
|             | 1. Compound of formula I      | 5                | 25    | 100    | 500    |
| 5           | 2. Lactose Anhydrous DTG      | 125              | 105   | 30     | 150    |
|             | 3. Sta-Rx 1500                | 6                | 6     | 6      | 30     |
|             | 4. Microcrystalline Cellulose | 30               | 30    | 30     | 150    |
|             | 5. Magnesium Stearate         | 1                | 1     | 1      | 1      |
|             | Total                         | 167              | 167   | 167    | 831    |

10 Manufacturing Procedure

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
4. Add item 5 and mix for three minutes; compress on a suitable press.

15 Capsule Formulation

| <u>Item</u> | <u>Ingredients</u>       | <u>mg/capsule</u> |       |        |        |
|-------------|--------------------------|-------------------|-------|--------|--------|
|             |                          | 5 mg              | 25 mg | 100 mg | 500 mg |
|             | 1. Compound of formula I | 5                 | 25    | 100    | 500    |
|             | 2. Hydrous Lactose       | 159               | 123   | 148    | ---    |
| 20          | 3. Corn Starch           | 25                | 35    | 40     | 70     |
|             | 4. Talc                  | 10                | 15    | 10     | 25     |
|             | 5. Magnesium Stearate    | 1                 | 2     | 2      | 5      |
|             | Total                    | 200               | 200   | 300    | 600    |

Manufacturing Procedure

- 25 1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

EXAMPLESSynthesis of intermediates of formula II

## Example A1

## (2-Amino-5-tert-butyl-phenyl)-phenyl-methanone

5        The title compound was prepared following the general procedure of method C. In a glass flask fitted with magnetic stir bar, rubber septum, thermometer, Hickmann-condenser, nitrogen-purged bubbler connected to a washing bottle containing 30 % NaOH, the content of a fresh ampoule of gallium (III) chloride (5 g, 29 mmol) was added at once and then dissolved by the addition of 1,2-dichloroethane (80 mL). This solution  
10        was cooled in ice, then 4-tert-butylaniline (36 mmol) was added slowly while keeping the temperature below 5 °C. Then the solution was cooled to -10 °C and a fresh 1 M solution of boron trichloride in dichloromethane (27 mL) was added via a syringe fitted with a teflon stop-cock while keeping the temperature below -5 °C. Finally benzonitrile was added (24 mmol) and the mixture was allowed to warm to 20 °C. The Hickmann-  
15        condenser was replaced by a normal reflux condenser and the reaction mixture was heated in an oil-bath (90 °C) over 1-2 h in order to distil off all the dichloromethane (a total of ca. 50 mL of distillate was collected) until the reflux temperature of 80 °C was achieved. Refluxing was continued for 14 h. The reaction mixture was cooled in ice and hydrolyzed slowly with water (40 mL) and then heated at 60-80 °C for 20-30 min. in  
20        order to hydrolyze the imine. The reaction mixture was cooled again and then extracted with dichloromethane and water. The crude product was purified by chromatography on silica gel in heptane/ethylacetate (4:1) and the purified product (yield 40%) analyzed by MS:  $m/z = 254$  (M+H).

## Example A2

## 25        (2-Amino-5-bromo-phenyl)-(4-fluoro-phenyl)-methanone

The title compound was prepared by reacting 4-bromoaniline and 4-methylsulfonyl benzonitrile following to the procedure of example A1. Yield 37%; MS:  $m/z = 294$  (M).

## Example A3

## (2-Amino-5-trifluoromethoxy-phenyl)-(4-chloro-phenyl)-methanone

30        The title compound was prepared by reacting 4-(trifluoromethoxy)aniline and 4-chloro benzonitrile following to the procedure of example A1, except that Aluminium

(III) chloride was used, that the reaction time was 4h and heptane/ethylacetate (2:1) was used for the chromatography. Yield 18%; MS:  $m/z = 315$  (M).

#### Example A4

##### (2-Amino-5-trifluoromethoxy-phenyl)-(3,4-dichloro-phenyl)-methanone

5 The title compound was prepared by reacting 4-(trifluoromethoxy)aniline and 3,4-dichloro benzonitrile following to the procedure of example A3, except that the reaction time was 16h. Yield 15%; MS:  $m/z = 408$  (M+OAc).

#### Example A5

##### (2-Amino-5-phenoxy-phenyl)-(4-chloro-phenyl)-methanone

10 The title compound was prepared by reacting 4-phenoxyaniline and 4-chloro benzonitrile following to the procedure of example A3, except that the reaction time was 14h and a gradient of heptane/ethylacetate was used for the chromatography. Yield 38%; MS:  $m/z = 324$  (M+H).

#### Example A6

##### 15 (2-Amino-5-trifluoromethoxy-phenyl)-phenyl-methanone

The title compound is known from FR 7666 and was prepared by reacting 4-(trifluoromethoxy)aniline and benzonitrile following to the procedure of example A1, except that the reaction time was 16h and heptane/ethylacetate (5:1) was used for the chromatography. Yield 40%; MS:  $m/z = 282$  (M+H).

20

#### Example A7

##### (2-Amino-5-trifluoromethoxy-phenyl)-(3-chloro-phenyl)-methanone

The title compound was prepared by reacting 4-(trifluoromethoxy)aniline and 3-chloro-benzonitrile following to the procedure of example A1. Yield 19%; MS:  $m/z = 315$  (M).

25

#### Example A8

##### (2-Amino-5-trifluoromethoxy-phenyl)-(4-methoxy-phenyl)-methanone

The title compound was prepared by reacting 4-phenoxyaniline and 4-methoxy benzonitrile following to the procedure of example A1, except that the reaction time was

19h and a gradient of heptane/ethylacetate was used for the chromatography. Yield 19%; MS:  $m/z = 312$  (M+H).

#### Example A9

##### (2-Amino-5-trifluoromethoxy-phenyl)-(4-fluoro-phenyl)-methanone

5        The title compound was prepared by reacting 4-(trifluoromethoxy)aniline and 4-fluorobenzonitrile following to the procedure of example A1. Yield 26%; MS:  $m/z = 299$  (M).

#### Example A10

##### (6-Amino-2,2-difluoro-benzo[1,3]dioxol-5-yl)-phenyl-methanone

10       The title compound was prepared by reacting 2,2-difluoro-5-aminobenzodioxole and benzonitrile following to the procedure of example A1. Yield 1.5%; MS:  $m/z = 366$  (M+OAc).

#### Example A11

##### (2-Amino-5-trifluoromethoxy-phenyl)-(3-trifluoromethoxy-phenyl)-methanone

15       The title compound was prepared by reacting 4-(trifluoromethoxy)aniline and 3-(trifluoromethoxy)benzonitrile following to the procedure of example A1. Yield 29%; MS:  $m/z = 365$  (M).

#### Example A12

##### (2-Amino-5-trifluoromethoxy-phenyl)-(3,4-difluoro-phenyl)-methanone

20       The title compound was prepared by reacting 4-(trifluoromethoxy)aniline and 3,4-difluorobenzonitrile following to the procedure of example A1. Yield 36%; MS:  $m/z = 317$  (M).

#### Example A13

##### (2-Amino-5-trifluoromethoxy-phenyl)-(4-methanesulfonyl-phenyl)-methanone

25       The title compound was prepared by reacting 4-(trifluoromethoxy)aniline and 4-methylsulfonylbenzonitrile following to the procedure of example A1. Yield 71%; MS:  $m/z = 359$  (M).

## Example A14

(2-Amino-5-trifluoromethoxy-phenyl)-(3-fluoro-4-methoxy-phenyl)-methanone

The title compound was prepared by reacting 4-(trifluoromethoxy)aniline and 3-methoxybenzonitrile following to the procedure of example A1. Yield 19%; MS: m/z =  
5 329 (M).

## Example A15

(2-Amino-5-bromo-phenyl)-(4-methanesulfonyl-phenyl)-methanone

The title compound was prepared by reacting 4-bromoaniline and 4-methylsulfonylbenzonitrile following to the procedure of example A1. Yield 51%; MS:  
10 m/z = 355 (M+H).

## Example A16

(2-Amino-5-bromo-phenyl)-phenyl-methanone

The title compound is known from US 20040127536 A1 and was prepared according to a method developed by D. Roche, K. Prasad, O. Repic, T. J. Blacklock,  
15 *Tetrahedron Lett.* 41, 2083-2085 (2000). 2-Aminobenzophenone (30g, 152mmol) was suspended in acetic acid (300mL). Potassium bromide (19.9g, 167mmol), sodium perborate tetrahydrate (28g, 183mmol) and ammonium molybdate tetrahydrate (1.5g) were added and stirring continued for 3 hours at 0°C. The dense yellow precipitate which formed was diluted with ice water (300mL) and then filtered off and washed with ice  
20 water and dried. One obtained 40.3 g (96%) of a yellow solid. MS: m/z = 276 (M).

## Example A17

(2-Amino-5-iodo-phenyl)-(4-methanesulfonyl-phenyl)-methanone

The title compound was prepared by reacting 4-iodoaniline and 4-methylsulfonylbenzonitrile following to the procedure of example A1. Yield 31 %; MS:  
25 m/z = 402 (M + H).

Synthesis of compounds of formula I according to the invention

## Example 1

1-(6-Bromo-2-ethyl-4-phenyl-quinolin-3-yl)-propan-1-one

The title compound was prepared according to the general procedure of method A.  
30 The (2-Amino-5-bromo-phenyl)-phenyl-methanone [example A16] (on 0.1 – 1 g scale)

and 3,5-heptanedione (1.5 equiv) and sodium tetrachloroaureate(III) dihydrate (0.025 equiv) were heated in parallel in a Radley carousel under nitrogen in ethanol (10 % w/w-solution of (2-Amino-5-bromo-phenyl)-phenyl-methanone) and reacted for 24h. The reaction mixture was evaporated to dryness and the residue purified by chromatography  
5 on silica gel in heptane, /ethyl acetate (20:1). Yield: 37 %. MS:  $m/z = 368$  (M).

#### Example 2

##### (6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-phenyl-methanone

The title compound was prepared from (2-Amino-5-bromo-phenyl)-phenyl-methanone [example A16] and 1-phenyl-1,3-butanedione, except that the residue was  
10 purified by spontaneous crystallization from the reaction mixture. Yield: 61 %; MS:  $m/z = 402$  (M+H).

#### Example 3

##### 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-2,2,2-trifluoro-ethanone

The title compound was prepared from (2-Amino-5-bromo-phenyl)-phenyl-  
15 methanone [example A16] and 1,1,1-trifluoro-2,4-pentanedione according to the procedure of example 1, except that heptane/ethyl acetate (10:1) was used. Yield: 50 %; MS:  $m/z = 392/394$  (M).

#### Example 4

##### 1-(6-Bromo-2-isobutyl-4-phenyl-quinolin-3-yl)-ethanone

The title compound was prepared from (2-Amino-5-bromo-phenyl)-phenyl-  
20 methanone [example A16] and 6-methyl-2,4-heptanedione according to the procedure of example 1. Yield: 9 %. MS:  $m/z = 381$  (M).

#### Example 5

##### 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-3-methyl-butan-1-one

The title compound was prepared from (2-Amino-5-bromo-phenyl)-phenyl-  
25 methanone [example A16] and 6-methyl-2,4-heptanedione according to the procedure of example 1. Yield: 55 %. MS:  $m/z = 381$  (M).

#### Example 6

##### 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-2,2-difluoro-ethanone

The title compound was prepared from (2-Amino-5-bromo-phenyl)-phenyl-methanone [example A16] and 1,1-difluoroacetylacetone according to the procedure of example 1, except that the residue was purified by chromatography on aminated silica gel with heptane/ethyl acetate (5:1). Yield: 36 %. MS:  $m/z = 377$  (M).

5

#### Example 7

1-[4-(4-Chloro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-ethanone

10

The title compound was prepared from (2-Amino-5-trifluoromethoxy-phenyl)-(4-chloro-phenyl)-methanone [example A3] and acetylacetone according to the method of example 1, except that heptane/ethyl acetate (1:2) was used. Yield: 61 %. MS:  $m/z = 379$  (M).

#### Example 8

1-(6-Bromo-2-isopropyl-4-phenyl-quinolin-3-yl)-2-methyl-propan-1-one

15

The title compound was prepared from (2-Amino-5-bromo-phenyl)-phenyl-methanone [example A16] and 2,6-dimethyl-3,5-heptanedione according to the method of example 1, except that the reaction time was of 96h and the residue was purified by chromatography on aminated silica gel with heptane/ethyl acetate (85:15). Yield: 46%. MS:  $m/z = 395/397$  (M).

#### Example 9

1-[4-(3,4-Dichloro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-ethanone

20

The title compound was prepared from (2-Amino-5-trifluoromethoxy-phenyl)-(3,4-dichloro-phenyl)-methanone [example A4] and acetylacetone according to the method of example 1, except that heptane/ethyl acetate (1:2). Yield: 59%. MS:  $m/z = 414$  (M).

#### Example 10

25

1-[4-(4-Chloro-phenyl)-2-methyl-6-phenoxy-quinolin-3-yl]-ethanone

30

The title compound was prepared from (2-Amino-5-phenoxy-phenyl)-(4-chloro-phenyl)-methanone [example A5] and acetylacetone according to the method of example 1, except that the solvent was isopropanol, the reaction time was of 16.5h and the residue was purified by spontaneous crystallization from the reaction mixture. Yield: 42 %; MS:  $m/z = 387$  (M).

## Example 11

2,2,2-Trifluoro-1-(2-methyl-4-phenyl-6-trifluoromethoxy-quinolin-3-yl)-ethanone

The title compound was prepared from (2-Amino-5-trifluoromethoxy-phenyl)-phenyl-methanone [example A6] and 1,1,1-trifluoro-2,4-pentanedione according to the  
5 procedure of example 1, except that the reaction time was of 44h and heptane/ethyl acetate (10:1) was used. Yield: 63 %; MS: m/z = 399 (M).

## Example 12

1-[4-(3-Chloro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-2,2,2-trifluoro-ethanone

10 The title compound was prepared from (2-Amino-5-trifluoromethoxy-phenyl)-(3-chloro-phenyl)-methanone [example A7] and 1,1,1-trifluoro-2,4-pentanedione according to the procedure of example 1, except that the solvent was isopropanol, the reaction time was of 60h and heptane/ethyl acetate (1:2) was used. Yield: 58 %; MS: m/z = 433 (M).

15

## Example 13

[4-(3-Chloro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-phenyl-methanone

The title compound was prepared from (2-Amino-5-trifluoromethoxy-phenyl)-(3-chloro-phenyl)-methanone [example A7] and benzoylacetone according to the procedure of example 1, except that the solvent was isopropanol, and heptane/ethyl acetate (1:2) was  
20 used. Yield: 57 %; MS: m/z = 441 (M).

## Example 14

1-[4-(4-Chloro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-2,2,2-trifluoro-ethanone

The title compound was prepared from (2-Amino-5-trifluoromethoxy-phenyl)-(4-chloro-phenyl)-methanone [example A3] and 1,1,1-trifluoro-2,4-pentanedione  
25 according to the procedure of example 1, except that the solvent was isopropanol, the reaction time was of 16h and heptane/ethyl acetate (1:2) was used. Yield: 34 %; MS: m/z = 433 (M).

## Example 15

30 1-[4-(3-Chloro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-ethanone

The title compound was prepared from (2-Amino-5-trifluoromethoxy-phenyl)-(3-chloro-phenyl)-methanone [example A7] and acetylacetone according to the procedure of example 1, except that the solvent was isopropanol, and heptane/ethyl acetate (1:2) was used. Yield: 55 %; MS: m/z = 380 (M+H).

5

## Example 16

2,2,2-Trifluoro-1-[4-(4-methoxy-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-ethanone

The title compound was prepared from (2-Amino-5-trifluoromethoxy-phenyl)-(4-methoxy-phenyl)-methanone [example A8] and 1,1,1-trifluoro-2,4-pentanedione according to the procedure of example 1, except that the solvent was isopropanol, the reaction time was of 17h and a gradient of heptane/ethyl acetate was used. Yield: 58 %; MS: m/z = 429 (M).

10

## Example 17

2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-ethanone

15

The title compound was prepared from (2-Amino-5-trifluoromethoxy-phenyl)-(4-fluoro-phenyl)-methanone [example A9] and 1,1,1-trifluoro-2,4-pentanedione according to the procedure of example 1, except that the solvent was isopropanol, the reaction time was of 16h and heptane/ethyl acetate (1:2) was used. Yield: 96 %; MS: m/z = 417 (M).

20

## Example 18

1-(6-tert-Butyl-2-methyl-4-phenyl-quinolin-3-yl)-2,2,2-trifluoro-ethanone

25

The title compound was prepared from (2-Amino-5-tert-butyl-phenyl)-phenyl-methanone [example A1] and 1,1,1-trifluoro-2,4-pentanedione according to the procedure of example 1, except that the solvent was isopropanol, the reaction time was of 16h and heptane/ethyl acetate (1:2) was used. Yield: 37 %; MS: m/z = 372 (M+H).

## Example 19

1-(2,2-Difluoro-6-methyl-8-phenyl-[1,3]dioxolo[4,5-g]quinolin-7-yl)-2,2,2-trifluoro-ethanone

The title compound was prepared from (6-Amino-2,2-difluoro-benzo[1,3]dioxol-5-yl)-phenyl-methanone [example A10] and 1,1,1-trifluoro-2,4-pentanedione according

30

to the procedure of example 1, except that the solvent was isopropanol, the reaction time was of 16h and heptane/ethyl acetate (1:2) was used. Yield: 30 %; MS:  $m/z = 396$  (M+H).

#### Example 20

1-[4-(3,4-Difluoro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-2,2,2-trifluoro-ethanone

5

The title compound was prepared from (2-Amino-5-trifluoromethoxy-phenyl)-(3,4-difluoro-phenyl)-methanone [example A12] and 1,1,1-trifluoro-2,4-pentanedione according to the procedure of example 1, except that the solvent was isopropanol, the reaction time was of 16h and heptane/ethyl acetate (1:2) was used. Yield: 36 %; MS:  $m/z = 435$  (M).

10

#### Example 21

2,2,2-Trifluoro-1-[4-(4-methanesulfonyl-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-ethanone

15

The title compound was prepared from (2-Amino-5-trifluoromethoxy-phenyl)-(4-methanesulfonyl-phenyl)-methanone [example A13] and 1,1,1-trifluoro-2,4-pentanedione according to the procedure of example 1, except that the solvent was isopropanol, the reaction time was of 16h and heptane/ethyl acetate (1:2) was used. Yield: 45 %; MS:  $m/z = 477$  (M).

#### Example 22

2,2,2-Trifluoro-1-[4-(3-fluoro-4-methoxy-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-ethanone

20

The title compound was prepared from (2-Amino-5-trifluoromethoxy-phenyl)-(4-methanesulfonyl-phenyl)-methanone [example A14] and 1,1,1-trifluoro-2,4-pentanedione according to the procedure of example 1, except that the solvent was isopropanol, the reaction time was of 16h and heptane/ethyl acetate (1:2) was used. Yield: 62 %; MS:  $m/z = 477$  (M).

25

#### Example 23

1-[6-Bromo-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone

30

The title compound was prepared from (2-Amino-5-bromo-phenyl)-(4-methanesulfonyl-phenyl)-methanone [example A15] and 1,1,1-trifluoro-2,4-

pentanedione according to the procedure of example 1, except that the solvent was isopropanol, the reaction time was of 16h and heptane/ethyl acetate (1:2) was used. Yield: 55 %; MS: m/z = 473 (M+H).

#### Example 24

5 1-[6-Bromo-4-(4-fluoro-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone

The title compound was prepared from (2-Amino-5-bromo-phenyl)-(4-fluoro-phenyl)-methanone [example A2] and 1,1,1-trifluoro-2,4-pentanedione according to the procedure of example 1, except that the solvent was isopropanol, the reaction time was of 16h and heptane/ethyl acetate (1:2) was used. Yield: 80 %; MS: m/z = 411/413 (M).

#### 10 Example 25

2,2,2-Trifluoro-1-(2-methyl-4-phenyl-6-piperidin-1-yl-quinolin-3-yl)-ethanone

The title compound was prepared according to the general procedure of method B. Following a methodology developed by J. P. Wolfe and S. L. Buchwald (*J. Org. Chem.* 2000, 65, 1144-1157) a screw-topped pressure-resistant glass vial (50 mL) equipped with  
15 a magnetic stirring bar was flushed with a stream of argon and charged with tris(dibenzylideneacetone)dipalladium chloroform complex (0.01 mmol), rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.02 mmol), dioxane (7.5 mL) and *tert.*-butanol (7.5 mL) and then stirred for 1 min before adding cesium carbonate (1.4 mmol), 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-2,2,2-trifluoro-ethanone [example 3] (1  
20 mmol), and piperidine (1.2 mmol). The glass vial was covered with a pressure-resistant seal, firmly locked by a screw-cap and heated with stirring in an oil bath at 120 °C during 2h. The glass vial was cooled in ice before opening, the reaction mixture was diluted with heptane (5 mL) and filtered through a plug of Dicalite filter-aid and rinsed with heptane. The filtrate was evaporated and the residue purified by chromatography on silica gel in  
25 heptane/ethyl acetate (4:1). Yield: 74 %; MS: m/z = 399 (M+H).

#### Example 26

2,2,2-Trifluoro-1-(2-methyl-6-morpholin-4-yl-4-phenyl-quinolin-3-yl)-ethanone

The title compound was prepared from 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-2,2,2-trifluoro-ethanone [example 3] and morpholine according to the procedure  
30 of example 25. Yield: 49 %; MS: m/z = 401 (M+H).

#### Example 27

2,2,2-Trifluoro-1-(2-methyl-4-phenyl-6-pyrrolidin-1-yl-quinolin-3-yl)-ethanone

The title compound was prepared from 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-2,2,2-trifluoro-ethanone [example 3] and pyrrolidine according to the procedure of example 25. Yield: 56 %; MS:  $m/z = 385$  (M+H).

#### Example 28

5      2,2,2-Trifluoro-1-[2-methyl-6-(2-methyl-pyrrolidin-1-yl)-4-phenyl-quinolin-3-yl]-ethanone

The title compound was prepared from 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-2,2,2-trifluoro-ethanone [example 3] and 2-methylpyrrolidine according to the procedure of example 25, except that the reaction time was of 16h. Yield: 21 %; MS:  $m/z$   
10      = 399 (M+H).

#### Example 29

2,2,2-Trifluoro-1-[2-methyl-6-(4-methyl-piperazin-1-yl)-4-phenyl-quinolin-3-yl]-ethanone

The title compound was prepared from 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-2,2,2-trifluoro-ethanone [example 3] and N-methylpiperazine according to the procedure of example 25, except that the reaction time was of 16h. Yield: 73 %; MS:  $m/z$   
15      = 414 (M+H).

#### Example 30

2,2,2-Trifluoro-1-[6-(3-hydroxy-pyrrolidin-1-yl)-2-methyl-4-phenyl-quinolin-3-yl]-ethanone  
20

The title compound was prepared from 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-2,2,2-trifluoro-ethanone [example 3] and 3-pyrrolidinol according to the procedure of example 25, except that the reaction time was of 16h. Yield: 92 %; MS:  $m/z = 401$  (M+H).

#### Example 31

25      2,2,2-Trifluoro-1-[6-(3-hydroxy-azetidin-1-yl)-2-methyl-4-phenyl-quinolin-3-yl]-ethanone

The title compound was prepared from 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-2,2,2-trifluoro-ethanone [example 3] and azetidin-3-ol according to the procedure of example 25, except that the reaction time was of 16h. Yield: 22 %; MS:  $m/z = 387$   
30      (M+H).

## Example 32

2,2,2-Trifluoro-1-[4-(4-methanesulfonyl-phenyl)-2-methyl-6-piperidin-1-yl-quinolin-3-yl]-ethanone

The title compound was prepared from 1-[6-Bromo-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone [example 23] and piperidine according to the procedure of example 25, except that the reaction time was of 16h. Yield: 36 %; MS:  $m/z = 277$  (M+H).

## Example 33

2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-2-methyl-6-piperidin-1-yl-quinolin-3-yl]-ethanone

The title compound was prepared from 1-[6-Bromo-4-(4-fluoro-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone [example 24] and piperidine according to the procedure of example 25, except that the reaction time was of 16h. Yield: 84 %; MS:  $m/z = 417$  (M+H).

Example 34

2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-2-methyl-6-morpholin-4-yl-quinolin-3-yl]-ethanone

The title compound was prepared from 1-[6-Bromo-4-(4-fluoro-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone [example 24] and morpholine according to the procedure of example 25, except that the reaction time was of 16h. Yield: 75 %; MS:  $m/z = 419$  (M+H).

## Example 35

2,2,2-Trifluoro-1-[4-(4-methanesulfonyl-phenyl)-2-methyl-6-pyrrolidin-1-yl-quinolin-3-yl]-ethanone

The title compound was prepared from 1-[6-Bromo-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone [example 23] and pyrrolidine according to the procedure of example 25, except that the reaction time was of 16h. Yield: 51 %; MS:  $m/z = 463$  (M+H).

## Example 36

2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-2-methyl-6-pyrrolidin-1-yl-quinolin-3-yl]-ethanone

The title compound was prepared from 1-[6-Bromo-4-(4-fluoro-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone [example 24] and pyrrolidine according to the procedure of example 25, except that the reaction time was of 16h. Yield: 64 %; MS:  $m/z = 403$  (M+H).

5

## Example 37

2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-6-(3-hydroxy-pyrrolidin-1-yl)-2-methyl-quinolin-3-yl]-ethanone

10

The title compound was prepared from 1-[6-Bromo-4-(4-fluoro-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone [example 24] and 3-pyrrolidinol according to the procedure of example 25, except that the reaction time was of 16h. Yield: 39 %; MS:  $m/z = 419$  (M+H).

## Example 38

2,2,2-Trifluoro-1-[6-(4-hydroxy-4-phenyl-piperidin-1-yl)-2-methyl-4-phenyl-quinolin-3-yl]-ethanone

15

The title compound was prepared from 1-[6-Bromo-4-(4-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone [example 24] and 4-hydroxy-4-phenylpiperidine according to the procedure of example 25, except that the reaction time was of 16h. Yield: 29 %; MS:  $m/z = 491$  (M+H).

## Example 39

20

2,2,2-Trifluoro-1-[6-(4-hydroxy-4-phenyl-piperidin-1-yl)-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-ethanone

25

The title compound was prepared from 1-[6-Bromo-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone [example 24] and 4-hydroxy-4-phenylpiperidine according to the procedure of example 25, except that the reaction time was of 16h. Yield: 17 %; MS:  $m/z = 569$  (M+H).

## Example 40

2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-6-(4-hydroxy-4-phenyl-piperidin-1-yl)-2-methyl-quinolin-3-yl]-ethanone

30

The title compound was prepared from 1-[6-Bromo-4-(4-fluoro-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone [example 24] and 4-hydroxy-4-

phenylpiperidine according to the procedure of example 25, except that the reaction time was of 16h. Yield: 32 %; MS:  $m/z = 509$  (M+H).

#### Example 41

2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-6-(3-hydroxy-azetidin-1-yl)-2-methyl-quinolin-3-yl]-ethanone

The title compound was prepared from 1-[6-Bromo-4-(4-fluoro-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone [example 24] and azetidin-3-ol according to the procedure of example 25, except that the reaction time was of 12h. Yield: 12 %; MS:  $m/z = 405$  (M+H).

#### Example 42

1-[6-Azepan-1-yl-4-(4-fluoro-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone

The title compound was prepared from 1-[6-Bromo-4-(4-fluoro-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone [example 24] and azepane according to the procedure of example 25, except that the reaction time was of 16h. Yield: 32 %; MS:  $m/z = 431$  (M+H).

#### Example 43

1-(6-Azepan-1-yl-2-methyl-4-phenyl-quinolin-3-yl)-2,2,2-trifluoro-ethanone

The title compound was prepared from 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-2,2,2-trifluoro-ethanone [example 3] and azepane according to the procedure of example 25, except that the reaction time was of 16h. Yield: 14 %; MS:  $m/z = 413$  (M+H).

#### Example 44

1-[6-(3-Dimethylamino-pyrrolidin-1-yl)-2-methyl-4-phenyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone

The title compound was prepared from 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-2,2,2-trifluoro-ethanone [example 3] and 3-(dimethylamino)pyrrolidine according to the procedure of example 25, except that the reaction time was of 16h and that ethyl acetate/methanol (9:1) was used. Yield: 37 %; MS:  $m/z = 428$  (M+H).

## Example 45

1-[6-(3-Dimethylamino-pyrrolidin-1-yl)-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone

The title compound was prepared from 1-[6-Bromo-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone [example 23] and 3-(dimethylamino)pyrrolidine according to the procedure of example 25, except that the reaction time was of 16h and that ethyl acetate/methanol (9:1) was used. Yield: 47 %; MS: m/z = 506 (M+H).

## Example 46

1-[6-(3-Dimethylamino-pyrrolidin-1-yl)-4-(4-fluoro-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone

The title compound was prepared from 1-[6-Bromo-4-(4-fluoro-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone [example 24] and 3-(dimethylamino)pyrrolidine according to the procedure of example 25, except that the reaction time was of 16h and that ethyl acetate/methanol (9:1) was used. Yield: 44 %; MS: m/z = 446 (M+H).

## Example 47

2,2,2-Trifluoro-1-[6-iodo-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-ethanone

The title compound was prepared from (2-Amino-5-iodo-phenyl)-(4-methanesulfonyl-phenyl)-methanone [example A17] and 1,1,1-trifluoro-2,4-pentanedione according to the procedure of example 1, except that the solvent was isopropanol, the reaction time was of 16 h and heptane/ethyl acetate (1:2) was used. Yield: 55 %; MS: m/z = 519 (M).

## Example 48

2,2,2-Trifluoro-1-[6-(4-hydroxy-4-methyl-piperidin-1-yl)-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-ethanone

The title compound was prepared from 1-[6-bromo-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone [example 23] and 4-methyl-

piperidin-4-ol according to the procedure of example 25. Yield: 14 %; MS:  $m/z = 507$  (M+H).

#### Example 49

2,2,2-Trifluoro-1-[4-(4-methanesulfonyl-phenyl)-6-(4-methoxy-piperidin-1-yl)-2-methyl-quinolin-3-yl]-ethanone

The title compound was prepared from 1-[6-bromo-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone [example 23] and 4-methoxy-piperidine according to the procedure of example 25. Yield: 14 %; MS:  $m/z = 507$  (M+H).

#### Example 50

[6-Bromo-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-cyclopropyl-methanone

The title compound was prepared from (2-Amino-5-bromo-phenyl)-(4-methanesulfonyl-phenyl)-methanone [example A15] and 1-cyclopropyl-1,3-butanedione according to the procedure of example 1, except that the solvent was isopropanol, the reaction time was of 16 h and heptane/ethyl acetate (1:2) was used. Yield: 47 %; MS:  $m/z = 443$  (M+H).

#### Example 51

Cyclopropyl-[4-(4-methanesulfonyl-phenyl)-2-methyl-6-morpholin-4-yl-quinolin-3-yl]-methanone

A tube placed under argon was charged with tris(dibenzylideneacetone)dipalladium chloroform complex (5 mg), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (5 mg) and cesium carbonate (110 mg, 0.33 mmol). [6-Bromo-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-cyclopropyl-methanone [example 50] (100 mg, 0.22 mmol) in t-BuOH (5ml) was added, followed by morpholine (24 mg, 0.27 mmol). The tube was sealed and heated at 110 °C for 6 hrs. The reaction mixture was cooled to 20 °C, diluted with heptane, and filtered through Celite and purified directly by flash chromatography on silica gel in heptane / AcOEt 80 : 20 to give a yellow solid (52 mg, 51%). MS:  $m/z = 451$  (M + H).

#### Example 52

1-[6-(3,3-Difluoro-piperidin-1-yl)-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone

The title compound was prepared from 1-[6-Bromo-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone [example 23] and 3,3-difluoropiperidine hydrochloride according to the procedure of example 51. Yield: 50 %; MS: m/z = 513 (M+H).

Example 53

2,2,2-Trifluoro-1-[4-(4-methanesulfonyl-phenyl)-2-methyl-6-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-quinolin-3-yl]-ethanone

The title compound was prepared from 1-[6-bromo-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone [example 23] and 8-oxa-3-aza-bicyclo[3.2.1]octane according to the procedure of example 51. Yield: 61 %; MS: m/z = 505 (M+H).

Example 54

Cyclopropyl-[4-(4-methanesulfonyl-phenyl)-2-methyl-6-piperidin-1-yl-quinolin-3-yl]-methanone

The title compound was prepared from [6-Bromo-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-cyclopropyl-methanone [example 50] and piperidine according to the procedure of example 51. Yield: 39 %; MS: m/z = 449 (M+H).

Example 55

[(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-cyclopropyl-methanone

The title compound was prepared from (2-amino-5-bromo-phenyl)-phenyl-methanone [example A16] and 1-cyclopropyl-1,3-butanedione according to the procedure of example 1, except that the solvent was isopropanol, the reaction time was of 16 h and heptane/ethyl acetate (1:2) was used. Yield: 75 %; MS: m/z = 366 (M).

Example 56

[6-Bromo-4-(4-fluoro-phenyl)-2-methyl-quinolin-3-yl]-cyclopropyl-methanone

The title compound was prepared from (2-amino-5-trifluoromethoxy-phenyl)-(4-fluorophenyl)-methanone [example A9] and 1-cyclopropyl-1,3-butanedione according to the procedure of example 1, except that the solvent was isopropanol, the

reaction time was of 16 h and heptane/ethyl acetate (1:2) was used. Yield: 76 %; MS: m/z = 384 (M).

#### Example 57

##### Cyclopropyl-(2-methyl-4-phenyl-6-piperidin-1-yl-quinolin-3-yl)-methanone

- 5        The title compound was prepared from [(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-cyclopropyl-methanone [example 55] and piperidine according to the procedure of example 51. Yield: 64 %; MS: m/z = 371 (M+H).

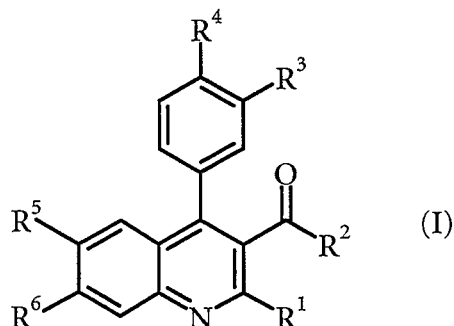
#### Example 58

##### 10        Cyclopropyl-(2-methyl-6-morpholin-4-yl-4-phenyl-quinolin-3-yl)-methanone

The title compound was prepared from [(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-cyclopropyl-methanone [example 55] and morpholine according to the procedure of example 51. Yield: 67 %; MS: m/z = 373 (M+H).

Claims

## 1. Compounds of formula I



5 wherein

R<sup>1</sup> is hydrogen, C<sub>1</sub>-C<sub>7</sub> alkyl, C<sub>1</sub>-C<sub>7</sub> haloalkyl, di(C<sub>1</sub>-C<sub>7</sub>)alkylamino, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, or 5 or 6 membered heterocycloalkyl;

R<sup>2</sup> is C<sub>1</sub>-C<sub>7</sub> alkyl, aryl, C<sub>1</sub>-C<sub>7</sub> alkoxy(C<sub>1</sub>-C<sub>7</sub>)alkyl, C<sub>1</sub>-C<sub>7</sub> haloalkyl or C<sub>3</sub>-C<sub>8</sub> cycloalkyl;

10 R<sup>3</sup>, R<sup>4</sup> are each independently hydrogen, halo, hydroxy, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> haloalkoxy, di(C<sub>1</sub>-C<sub>7</sub>)alkylamino, C<sub>1</sub>-C<sub>7</sub> alkylsulfonyl, or 5 or 6 membered heterocycloalkyl;

R<sup>5</sup> is hydrogen, halo, C<sub>1</sub>-C<sub>7</sub> alkyl, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> haloalkoxy, or aryloxy, or is -NR<sup>7</sup>R<sup>8</sup> wherein R<sup>7</sup> and R<sup>8</sup> are C<sub>1</sub>-C<sub>7</sub> alkyl, or R<sup>7</sup> and R<sup>8</sup> may, together with the nitrogen atom to which they are attached, form or a 4 to 7 membered heterocycloalkyl group which may be substituted by one or more substituent(s) selected from the group consisting of halo, C<sub>1</sub>-C<sub>7</sub> alkyl, C<sub>1</sub>-C<sub>7</sub> alkoxy, hydroxy, phenyl and di(C<sub>1</sub>-C<sub>7</sub>)alkylamino;

15 R<sup>6</sup> is hydrogen or together with R<sup>5</sup> may form a 5 or 6 membered heterocycloalkyl group which may be substituted by one or more halogen;

20 and pharmaceutically acceptable acid addition salts thereof,

excluding the following compounds:

1-(6-Chloro-2-methyl-4-phenyl-quinolin-3-yl)-ethanone;

1-(6-Bromo-4-phenyl-2-piperidin-1-yl-quinolin-3-yl)-ethanone;

25 1-[4-(4-Chloro-phenyl)-2-methyl-quinolin-3-yl]-ethanone;

1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-ethanone;

1-(2,6-Dimethyl-4-phenyl-quinolin-3-yl)-ethanone; and

1-(2-Methyl-4-phenyl-6-trifluoromethoxy-quinolin-3-yl)-ethanone.

## 2. Compounds of formula I according to claim 1, wherein

30 R<sup>1</sup> is C<sub>1</sub>-C<sub>7</sub> alkyl;

- R<sup>2</sup> is C<sub>1</sub>-C<sub>7</sub> alkyl, phenyl, C<sub>1</sub>-C<sub>7</sub> haloalkyl;  
 R<sup>3</sup>, R<sup>4</sup> are each independently hydrogen, halo, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> alkylsulfonyl,  
 R<sup>5</sup> is halo, C<sub>1</sub>-C<sub>7</sub> haloalkoxy, aryloxy, or -NR<sup>7</sup>R<sup>8</sup> wherein R<sup>7</sup> and R<sup>8</sup> are C<sub>1</sub>-C<sub>7</sub> alkyl,  
 may, together with the nitrogen atom to which they are attached, form or a 4 to  
 5 7 membered heterocycloalkyl group which may be substituted by one or more  
 substituent(s) selected from the group consisting of halo, C<sub>1</sub>-C<sub>7</sub> alkyl, hydroxy,  
 C<sub>1</sub>-C<sub>7</sub> alkoxy, phenyl and di(C<sub>1</sub>-C<sub>7</sub>)alkylamino;  
 R<sup>6</sup> is hydrogen or together with R<sup>5</sup> may form a 5 or 6 membered heterocycloalkyl  
 group which may be substituted by one or more halogen;  
 10 and pharmaceutically acceptable acid addition salts thereof.

3. Compounds of formula I according to claim 1, wherein R<sup>2</sup> is C<sub>1</sub>-C<sub>7</sub> alkyl.

4. Compounds of formula I according to claim 3, wherein the compounds are selected from the group consisting of:

- 1-(6-Bromo-2-ethyl-4-phenyl-quinolin-3-yl)-propan-1-one;  
 15 1-(6-Bromo-2-isobutyl-4-phenyl-quinolin-3-yl)-ethanone;  
 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-3-methyl-butan-1-one;  
 1-[4-(4-Chloro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-ethanone;  
 1-(6-Bromo-2-isopropyl-4-phenyl-quinolin-3-yl)-2-methyl-propan-1-one;  
 1-[4-(3,4-Dichloro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-ethanone;  
 20 1-[4-(4-Chloro-phenyl)-2-methyl-6-phenoxy-quinolin-3-yl]-ethanone; and  
 1-[4-(3-Chloro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-ethanone.

5. Compounds of formula I according to claim 1, wherein R<sup>2</sup> is C<sub>1</sub>-C<sub>7</sub> haloalkyl.

6. Compounds of formula I according to claim 5, wherein the compounds are selected from the group consisting of:

- 25 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-2,2,2-trifluoro-ethanone;  
 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-2,2-difluoro-ethanone;  
 2,2,2-Trifluoro-1-(2-methyl-4-phenyl-6-trifluoromethoxy-quinolin-3-yl)-ethanone;  
 1-[4-(3-Chloro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-2,2,2-trifluoro-  
 ethanone;  
 30 1-[4-(4-Chloro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-2,2,2-trifluoro-  
 ethanone;  
 2,2,2-Trifluoro-1-[4-(4-methoxy-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-  
 ethanone;

- 2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-ethanone;
- 1-(6-tert-Butyl-2-methyl-4-phenyl-quinolin-3-yl)-2,2,2-trifluoro-ethanone;
- 1-(2,2-Difluoro-6-methyl-8-phenyl-[1,3]dioxolo[4,5-g]quinolin-7-yl)-2,2,2-trifluoro-
- 5 ethanone;
- 1-[4-(3,4-Difluoro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-2,2,2-trifluoro-ethanone;
- 2,2,2-Trifluoro-1-[4-(4-methanesulfonyl-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-ethanone;
- 10 2,2,2-Trifluoro-1-[4-(3-fluoro-4-methoxy-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-ethanone;
- 2,2,2-Trifluoro-1-(2-methyl-4-phenyl-6-piperidin-1-yl-quinolin-3-yl)-ethanone;
- 2,2,2-Trifluoro-1-(2-methyl-6-morpholin-4-yl-4-phenyl-quinolin-3-yl)-ethanone;
- 2,2,2-Trifluoro-1-(2-methyl-4-phenyl-6-pyrrolidin-1-yl-quinolin-3-yl)-ethanone;
- 15 2,2,2-Trifluoro-1-[2-methyl-6-(2-methyl-pyrrolidin-1-yl)-4-phenyl-quinolin-3-yl]-ethanone;
- 2,2,2-Trifluoro-1-[2-methyl-6-(4-methyl-piperazin-1-yl)-4-phenyl-quinolin-3-yl]-ethanone;
- 2,2,2-Trifluoro-1-[6-(3-hydroxy-pyrrolidin-1-yl)-2-methyl-4-phenyl-quinolin-3-yl]-
- 20 ethanone;
- 2,2,2-Trifluoro-1-[6-(3-hydroxy-azetidin-1-yl)-2-methyl-4-phenyl-quinolin-3-yl]-ethanone;
- 1-[6-Bromo-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone;
- 25 1-[6-Bromo-4-(4-fluoro-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone;
- 2,2,2-Trifluoro-1-[4-(4-methanesulfonyl-phenyl)-2-methyl-6-piperidin-1-yl-quinolin-3-yl]-ethanone;
- 2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-2-methyl-6-piperidin-1-yl-quinolin-3-yl]-ethanone;
- 30 2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-2-methyl-6-morpholin-4-yl-quinolin-3-yl]-ethanone;
- 2,2,2-Trifluoro-1-[4-(4-methanesulfonyl-phenyl)-2-methyl-6-pyrrolidin-1-yl-quinolin-3-yl]-ethanone;
- 2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-2-methyl-6-pyrrolidin-1-yl-quinolin-3-yl]-
- 35 ethanone;
- 2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-6-(3-hydroxy-pyrrolidin-1-yl)-2-methyl-quinolin-3-yl]-ethanone;

- 2,2,2-Trifluoro-1-[6-(4-hydroxy-4-phenyl-piperidin-1-yl)-2-methyl-4-phenyl-quinolin-3-yl]-ethanone;
- 2,2,2-Trifluoro-1-[6-(4-hydroxy-4-phenyl-piperidin-1-yl)-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-ethanone;
- 5 2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-6-(4-hydroxy-4-phenyl-piperidin-1-yl)-2-methyl-quinolin-3-yl]-ethanone;
- 2,2,2-Trifluoro-1-[4-(4-fluoro-phenyl)-6-(3-hydroxy-azetidin-1-yl)-2-methyl-quinolin-3-yl]-ethanone;
- 1-[6-Azepan-1-yl-4-(4-fluoro-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone;
- 10 1-(6-Azepan-1-yl-2-methyl-4-phenyl-quinolin-3-yl)-2,2,2-trifluoro-ethanone;
- 1-[6-(3-Dimethylamino-pyrrolidin-1-yl)-2-methyl-4-phenyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone;
- 1-[6-(3-Dimethylamino-pyrrolidin-1-yl)-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone;
- 15 1-[6-(3-Dimethylamino-pyrrolidin-1-yl)-4-(4-fluoro-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone;
- 2,2,2-Trifluoro-1-[6-iodo-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-ethanone;
- 2,2,2-Trifluoro-1-[6-(4-hydroxy-4-methyl-piperidin-1-yl)-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-ethanone;
- 20 2,2,2-Trifluoro-1-[4-(4-methanesulfonyl-phenyl)-6-(4-methoxy-piperidin-1-yl)-2-methyl-quinolin-3-yl]-ethanone;
- 1-[6-(3,3-Difluoro-piperidin-1-yl)-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-2,2,2-trifluoro-ethanone; and
- 25 2,2,2-Trifluoro-1-[4-(4-methanesulfonyl-phenyl)-2-methyl-6-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-quinolin-3-yl]-ethanone.

7. Compounds of formula I according to claim 1, wherein  $R^2$  is cycloalkyl.

8. Compounds of formula I according to claim 7, wherein the compounds are selected from the group consisting of:

- 30 6-Bromo-4-(4-methanesulfonyl-phenyl)-2-methyl-quinolin-3-yl]-cyclopropyl-methanone;
- Cyclopropyl-[4-(4-methanesulfonyl-phenyl)-2-methyl-6-morpholin-4-yl-quinolin-3-yl]-methanone;
- Cyclopropyl-[4-(4-methanesulfonyl-phenyl)-2-methyl-6-piperidin-1-yl-quinolin-3-yl]-methanone;
- 35 3-yl]-methanone;

[(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-cyclopropyl-methanone;  
 [6-Bromo-4-(4-fluoro-phenyl)-2-methyl-quinolin-3-yl]-cyclopropyl-methanone;  
 Cyclopropyl-(2-methyl-4-phenyl-6-piperidin-1-yl-quinolin-3-yl)-methanone and  
 Cyclopropyl-(2-methyl-6-morpholin-4-yl-4-phenyl-quinolin-3-yl)-methanone.

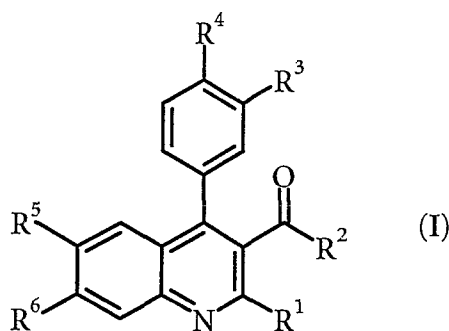
9. Compounds of formula I according to claim 1, wherein  $R^2$  is phenyl.

10. Compounds of formula I according to claim 9, wherein the compounds are selected from the group consisting of:

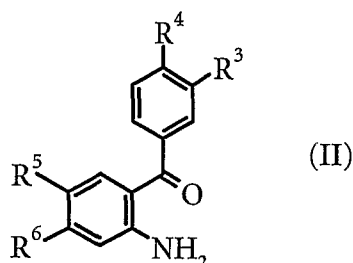
(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-phenyl-methanone; and

[4-(3-Chloro-phenyl)-2-methyl-6-trifluoromethoxy-quinolin-3-yl]-phenyl-methanone.

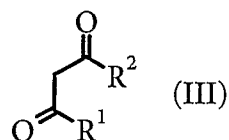
11. A process for the preparation of a compound of formula I



comprising the step of reacting a compound of formula II



with a compound of formula III

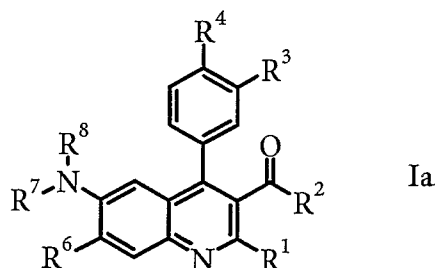


to give the compound of formula I;

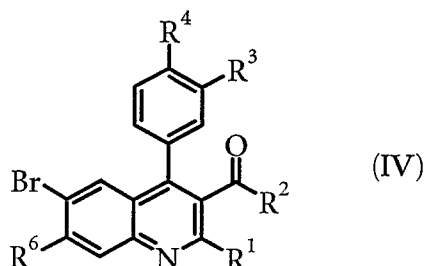
wherein  $R^1$  to  $R^6$  are as defined for formula I;

and if desired, converting the compound of formula I obtained into a pharmaceutically acceptable acid addition salt.

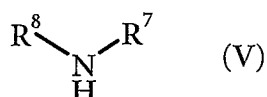
12. A process for the preparation of a compound of formula Ia



comprising the steps of reacting a compound of formula IV



with a compound of formula V



5

to give the compound of formula Ia;

wherein R<sup>1</sup> to R<sup>8</sup> are as defined in claim 1;

and if desired, converting the compound of formula Ia obtained into a pharmaceutically acceptable acid addition salt.

10        13. A compound of formula I, prepared according to the process of any one of claim 11 or 12.

14. A medicament containing a compound of formula I according to any one of claims 1 to 10.

15        15. A medicament according to claim 14, wherein the medicament is useful in the control or prevention of illnesses, especially of illnesses and disorders comprising anxiety, depression, epilepsy, schizophrenia, cognitive disorders, spasticity and skeletal muscle rigidity, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, cerebral palsy, neuropathic pain and craving associated with cocaine and nicotine, psychosis, panic disorder, posttraumatic stress disorders or gastro-intestinal disorders.

20        16. The use of a compound of formula I according to any one of claims 1 to 10 or of a compound selected from the group consisting of:

1-(6-Chloro-2-methyl-4-phenyl-quinolin-3-yl)-ethanone;

1-(6-Bromo-4-phenyl-2-piperidin-1-yl-quinolin-3-yl)-ethanone;

- 1-[4-(4-Chloro-phenyl)-2-methyl-quinolin-3-yl]-ethanone;  
1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-ethanone;  
1-(2,6-Dimethyl-4-phenyl-quinolin-3-yl)-ethanone; and  
1-(2-Methyl-4-phenyl-6-trifluoromethoxy-quinolin-3-yl)-ethanone,  
5 or of their pharmaceutically acceptable salts, for the manufacture of a medicament.

17. The use according to claim 16, wherein the medicament is useful in the control  
or prevention of illnesses, especially of illnesses and disorders comprising anxiety,  
depression, epilepsy, schizophrenia, cognitive disorders, spasticity and skeletal muscle  
rigidity, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, cerebral palsy,  
10 neuropathic pain and craving associated with cocaine and nicotine, psychosis, panic  
disorder, posttraumatic stress disorders or gastro-intestinal disorders.

18. A compound of formula I, a process for the preparation of a compound of  
formulae I or Ia, a medicament containing a compound of formula I and a use of a  
compound of formula I for the manufacture of a medicament as claimed in claims 1 to 17  
15 and as described above.